RETROSPECTIVE ASSESSMENT OF NEONETAL SEPSIS CASES IN GOVERNMENT HOSPITAL TIRUPUR

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DECLARATION

The research work embodied in this dissertation work entitled " **RETROSPETIVE ASSESSMENT OF NEONATAL SEPSIS CASES IN GOVERNMENT HOSPITAL TIRUPUR"** was carried out by me in the department of pharmacy practice, the erode college of pharmacy, erode, under the direct supervision of **Dr.R. SenthilSelvi., M.Pharm., Ph.D.,** the erode college of pharmacy, erode. Thos dissertation submitted to **THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY, CHENNAI,** as a partial fulfillment for the award of **degree in Master of Pharmacy** in pharmacy practice during the academic year 2017-2018. The work is original and has not been submitted in part or full for the award of any degree or diploma of this or any other university.

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EVALUATION CERTIFICATE

This is to certify that dissertation work entitled "**RETROSPECTIVE ASSESSMENT OF NEONATAL SEPSIS CASES IN GOVERNMENT HOSPITAL TIRUPUR"** Submitted by **REG NO: 261640403** to THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI, in partial fulfillment for the degree of **MASTER OF PHARMACY** is a bonafide thesis work carried out by the candidate at the department of pharmacy practice, The Erode college of pharmacy and Research institute, erode, was evaluated by us during the academic year **2017-2018.**

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ABBREVIATIONS

EOS	Early Onset Sepsis
LOS	Late Onset Sepsis
TLC	Total Leukocyte Count
CRP	C -Reactive Protein
ESR	Erythrocyte Sedimentation Rate
CSF	Cerebro Spinal Fluid
GBS	Group B Streptococci
NICU	Neonatal Intensive Care Unit
UTI	Urinary Tract Infection
ROM	Rupture Of Membrane
PROM	Premature Rupture Of Membrane
TNF	Tissue Necroting Factor
INF	Interferon
IL	Interleukin
PAF	Platelet Activating Factor
PAI	Plasminogen Activated Inhibitor
LP	Lumbar Puncture
IV	Intravenous
TPN	Total Parentral Nutrition
ET	Exchange Transfusion

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I.INTRODUCTION

NEONATAL SEPSIS

Neonatal infections currently cause about 1.6 million deaths annually in developing countries. Sepsis and meningitis are responsible for most of these deaths. Resistance to commonly used antibiotics is emerging and constitutes an important problem world wide.

Sepsis is the commonest cause of neonatal mortality; it is responsible for about 30-50% of the total neonatal deaths in developing countries.[1]It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes. Sepsis related mortality is largely preventable with prevention of sepsis itself, timely recognition, rational antimicrobial therapy and aggressive supportive care.[2]

Neonatal sepsis is a type of neonatal infection and specifically refers to the presence in a newborn baby of a bacterial blood stream infection (BSI) (such as meningitis, pneumonia, pyelonephritis, or gastroenteritis) in the setting of fever. Older textbooks may refer to neonatal sepsis as "sepsis neonatorum". Criteria with regards to hemodynamic compromise or respiratory failure are not useful clinically because these symptoms often do not arise in neonates until death is imminent and unpreventable. Neonatal sepsis is divided into two categories: early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS refers to sepsis presenting in the first 7 days of life[3](although some refer to EOS as within the first 72 hours of life), with LOS referring to presentation of sepsis after 7 days (or 72 hours, depending on the system used). neonatal sepsis is the single most important cause of neonatal death in hospital as well as community in developing country.

It is difficult to clinically exclude sepsis in newborns less than 90 days old that have fever (defined as a temperature > 38 °C (100.4 °F). Except in the case of obvious acute viral bronchiolitis, the current practice in newborns less than 30 days old is to perform a

complete workup including complete blood count with differential, blood culture, urinalysis, urine culture, and cerebrospinal fluid (CSF) studies and CSF culture, admit the newborn to the hospital, and treat empirically for serious bacterial infection for at least 48 hours until cultures are demonstrated to show no growth. Attempts have been made to see whether it is possible to risk stratify newborns in order to decide if a newborn can be safely monitored at home without treatment despite having a fever. One such attempt is the Rochester criteria.

DEFINITION

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. It encompasses various systemic infections of the new-born such as septicaemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections.[4]

The newest definition of sepsis has recently been published. In 2016, the Third International Consensus Definitions Task Force (Sepsis-3) defined sepsis as "life-threatening organ dysfunction due to a dysregulated host response to infection." The new criteria are based on just three symptoms.

- Altered mental status
- Fast respiratory rate (> 22 breaths/minute)
- Low blood pressure (≤ 100 mm Hg systolic)

According to National Neonatal Forum of India sepsis has defined as follows: [5]

Probable (Clinical) Sepsis: In an infant having clinical picture suggestive of septicaemia, if there is the presence of any one of the following criteria:

- Existence of predisposing factors: maternal fever or foul smelling liquor or prolonged rupture of membranes (>24 hrs) or gastric polymorphs (>5 per high power field).
- Positive septic screen - presence of two of the four parameters namely, TLC (< 5000/mm), band to total polymorph nuclear cells ratio of >0.2, absolute neutrophil count < 1800/cumm, C-reactive protein (CRP) >1mg/dl and micro ESR > 10 mm-first hour.
- Radiological evidence of pneumonia.

CLASSIFICATION

Neonatal sepsis can be classified into two major categories depending up on the onset of symptoms[6]

Early onset sepsis (EOS): It presents within the first 72 hours of life. In severe cases, the neonate may be symptomatic at birth. Infants with EOS usually present with respiratory distress and pneumonia. The source of infection is generally the maternal genital tract. Some maternal/ perinatal conditions have been associated with an increased risk of EOS. Knowledge about these potential risk factors would help in early diagnosis of sepsis. Based on the studies from India, the following risk factors seem to be associated with an increased risk of early onset sepsis.[6,7]

1. Low birth weight (<2500 grams) or prematurity.
2. Febrile illness in the mother with evidence of bacterial infection within 2 weeks prior to delivery
3. Foul smelling and/or meconium stained liquor
4. Rupture of membranes >24 hours
5. Single unclean or > 3 sterile vaginal examination(s) during labour
6. Prolonged labor (sum of 1st and 2nd stage of labor > 24 hrs

7. Perinatal asphyxia (Apgar score <4 at 1 minute) Presence of foul smelling liquor or three of the above mentioned risk factors warrant initiation of antibiotic treatment. Infants with two risk factors should be investigated and then treated accordingly.

Late onset sepsis (LOS):LONS occurs at 4-90 days of life and is acquired from the care giving environment [8]. The incidence ranges from 1.87 to 5.42 per 1,000 live births [9]. It usually presents after 72 hours of age. The source of infection in LOS is either nosocomial (hospital-acquired) or community-acquired and neonates usually present with septicaemia, pneumonia or meningitis.Various factors that predispose to an increased risk of nosocomial sepsis include low birth weight, prematurity, admission in intensive care unit, mechanical ventilation, invasive procedures, administration of parenteral fluids, and use of stock solutions. Factors that might increase the risk of community-acquired LOS include poor hygiene, poor cord care, bottle-feeding, and prelacteal feeds. In contrast, breastfeeding helps in prevention of infections. In LOS most common clinical manifestations are: meningitis (30-40%), bacteraemia (40%), and septic arthritis (5-10%).[10]

EARLY VS LATE ONSET SEPSIS

	EARLY	**LATE**
Onset	Upto 72 hrs	After 72 hrs
Source	Maternal	Postnatal environment
Presentation	Fulminant multisystem Pneumonia frequent	Slowly progressive,focal Meningitis frequent
Mortality	15-50%	10-20%

SIGNS AD SYMPTOMS OF NEONATAL SEPSIS[11]

The clinical signs and symptoms of sepsis in the neonate are very different from the adult. These are divided into early and late signs and symptoms. Often, symptoms in the early stage are non-specific, making it difficult to diagnose.

The **Early Stage** of sepsis development is also known as "warm shock." The main symptoms are from a decrease in systemic vascular resistance due to vasodilatation.

The **Late Stage** of sepsis development is caused from the body being unable to meet the oxygen demands of tissues. Tissue damage and lactic acidosis can occur, and this is now a hypovolemic state.

SIGNS OF NEONATAL SEPSIS

- Cold to touch (hypothermia)
- Poor perfusion (CRT)
- Hypotension
- Renal failure
- Sclerema
- Bulging fontanels, neck retraction
- Poor weight gain

SYMPTOMS OF NEONATAL SEPSIS

GIT

- Vomiting
- Diarrhoea
- Abdominal distension

HAEMATOLOGICAL

- Bleeding
- Jaundice

SKIN

- Rashes
- Purpura
- Pustules

CNS

- Lethargy
- Refusal to suckle
- Limp not arousable
- Poor or high pitched cry
- Irritable, Seizures

CVS

- Pallor
- Cyanosis
- Cold clammy skin

RESPIRATORY

- Tachypnea
- Apnea
- Grunt
- Retractions

CLINICAL FEATURES OF SEVERE INFECTIONS

According to WHO young infant study 2003 the following are the clinical features of severe neonatal sepsis.

1. Feeding ability reduced
2. No spontaneous movement
3. Temperature >380ºC
4. Prolonged capillary refill time
5. Lower chest wall indrawing
6. Resp. rate > 60/minute
7. Grunting
8. Cyanosis
9. convulsions

RISK FACTORS FOR NEONATAL SEPSIS[11,12]

Following are the major risk factors associated with neonatal sepsis.

Maternal

- No prenatal care
- Malnutrition
- Low socioeconomic status
- Substance abuse
- Fever
- Active urinary tract infection (UTI)
- Chorioamnionitis
- Positive or unknown Group B Stephilococus.

- Premature rupture of membranes (ROM) or premature labour<37 weeks
- Prolonged ROM >24 hours
- Prolonged or difficult labour
- Multiple pregnancies

Neonatal [13]

- Prematurity
- Low birth weight
- Congenital anomalies (especially ones that disrupt first line of defence, such as gastroschisis)
- Male gender
- Newborn errors of metabolism
- Asphyxia/fetal distress
- Meconium aspiration

Environmental Risk Factors

- Resuscitation
- Invasive procedures
  - Length of hospitalization
  - Use of anti-biotics

ETIOLOGY

Etiological Factors Causing Sepsis

PROM: Premature rupture of membrane is one of the most common causes of neonatal sepsis. Once the membranes have been ruptured for >18 hours, the risk of sepsis in the neonate increases approximately 10 fold over baseline, to a rate of 1% for proven and 2% for suspected sepsis. The risk of proven sepsis with PROM in the preterm infant (PPROM) is increases to 4%–6%. A 5- minute Apgar score <6 also raise the sepsis risk to 3%– 4%.[14]

Chorioamnionitis/Maternal fever: range of neonatal sepsis when chorioamnionitis is present is 3%–20%, with The problem with chorioamnionitis is one of diagnostic definition in day-to- day clinical practice, with wide variability and interpretation among clinicians. The generally accepted definition is presence of maternal fever >100.4_F with two or more of the following findings: fetal tachycardia, uterine tenderness, foul vaginal discharge, or maternal leucocytosis. The reported an odds ratio of 6:42 (2.32–17.8).[15] Maternal fever without signs of chorioamnionitis also raises the risk of sepsis, but may be confounded by non-infectious causes of maternal fever such as dehydration or epidural anaesthesia.

Maternal colonization with group B Streptococcus (GBS): Maternal colonization with GBS without clinical complications and without antibiotic prophylaxis carries a neonatal sepsis risk of 1%; the risk rises to a best estimate of 4%–7% in the presence of clinical complications such as PROM, maternal fever, or prematurity; and as high as 20% in the presence of chorioamnionitis.[16,17] Risk factors for maternal GBS colonization include African American race, maternal age of <20 years, low parity, and diabetes.[18]

Prematurity: Prematurity and neonatal sepsis increases the risk for premature infants. Preterm infants are more likely to require invasive procedures, such as umbilical (CMV), herpes simplex virus (HSV), hepatitis B, toxoplasmosis, Mycobacterium tuberculosis,

Campylobacter fetus, and Listeria species. Premature infants have less immunologic ability to resist and combat infection.

This leads to infection with common organisms such as coagulase- negative staphylococci an organism usually not associated with severe sepsis.[19]

Maternal urinary tract infection (UTI): As noted, GBS bacteruria is a risk factor for sepsis. Likewise, UTI of any cause raises the risk of sepsis in the neonate, in part due to raising the risk of prematurity and chorioamnionitis.[20]

COMMON MICRO ORGANISMS CAUSING NEONTAL SEPSIS

The microorganisms most commonly associated with **early-onset** infection include the following .

- Group B Streptococcus (GBS)
- Escherichia coli
- Coagulase-negative staphylo cocus
- Haemophyllus influenza
- Listeria monocytogens

Organisms that have been implicated in causing **late-onset** sepsis include the following:

- Staphylococcus aureus[21,22-23,24]
- Coagulase-negative Staphylococcus[25]
- E coli
- Klebsiella
- Pseudomonas
- Enterobacter
- Candida
- GBS

- Serratia
- Acinetobacter
- Anaerobes

Group B streptococcus (GBS) is generally rare[26,27] or not seen at all, although maternal rectovaginal carriage rates of GBS may be similar to those recorded in developed countries.[28] In most of the African studies,[29] the incidence is low, with the exception of South Africa. In Asia[30] GBS is also reported to be extremely rare. In South America[31]GBS incidence is comparable to the West.

PATHOPHYSIOLOGY

Sepsis disturbs the harmonious balance that exists in healthy state between pro and anti inflammatory cytokines, coagulant and anti-coagulant elements, and between endothelial integrity and circulating cells. Infection by a pathogen disturbs this balance. Body deals with infection by activating many of host defence systems simultaneously to regain the balance. If the balance is regained then outcome is recovery, but if this balance is either not restored or accentuated then the outcome is poor. During the inflammatory process, cells of the haemopoetic system and immune modulating mediators are activated to move towards the affected site for destroying the pathogen. Activation of the inflammatory response is initiated by release of endotoxin (LPS) from Gram-negative or exotoxins (peptoglycans) from Gram-positive organism and other cellular antigenic components of the pathogens. From then on initiation and maintenance of inflammatory cascade result from a complex array of interactions between pathogen and host defence systems.[32,33] Leukocyte activation in particular that of macrophage and mononuclear cells brings about transcriptional changes

related to immune activation and signal transduction dependent on genetic predisposition and bacterial characteristics.[34] Transcription factors up-regulate the production of pro-inflammatory cytokines such as TNF-α, INFα, IL-6 and anti-inflammatory cytokines IL-10, IL- 18.[35] Substances released from pathogens and damaged tissues up regulate adhesion molecules on the vascular endothelium arresting and activating rolling neutrophils on to the vascular wall. Activated neutrophils change shape to pass through the vessel wall and move to the site of infection where they phagocytosis C3b coated organisms. Mediators like complement, chemokine, products of prostaglandin metabolism, and leukotrines all contribute towards recruitment of inflammatory cells to the site of infection. Preterm VLBW infants are either deficient or inefficient in generating these responses in an adequate manner. In particular, poor transmigration of neutrophils and chemotaxis results in lack of localization of infection hence the neonate is prone to more frequent generalised blood stream infections. The process of activated inflammatory cells producing range of pro-inflammatory mediators like TNF-α, IL-1, IL-6, and IL-8, platelet activating factor (PAF), leukotriene and thromboxane A2 accentuate endothelial damage.[36]Leak of granulocytes and other mediators through the injured endothelium cause the clinical effects seen in sepsis which can be enumerated by the synonym CHAOS;

C = Cardiovascular; changes in the micro and macro- circulation, decrease vascular tone, poor tissue perfusion, hypotension and organ failure.

H = Haemopoetic; anaemia, neutropenia, disseminated intra-vascular coagulation (DIC).

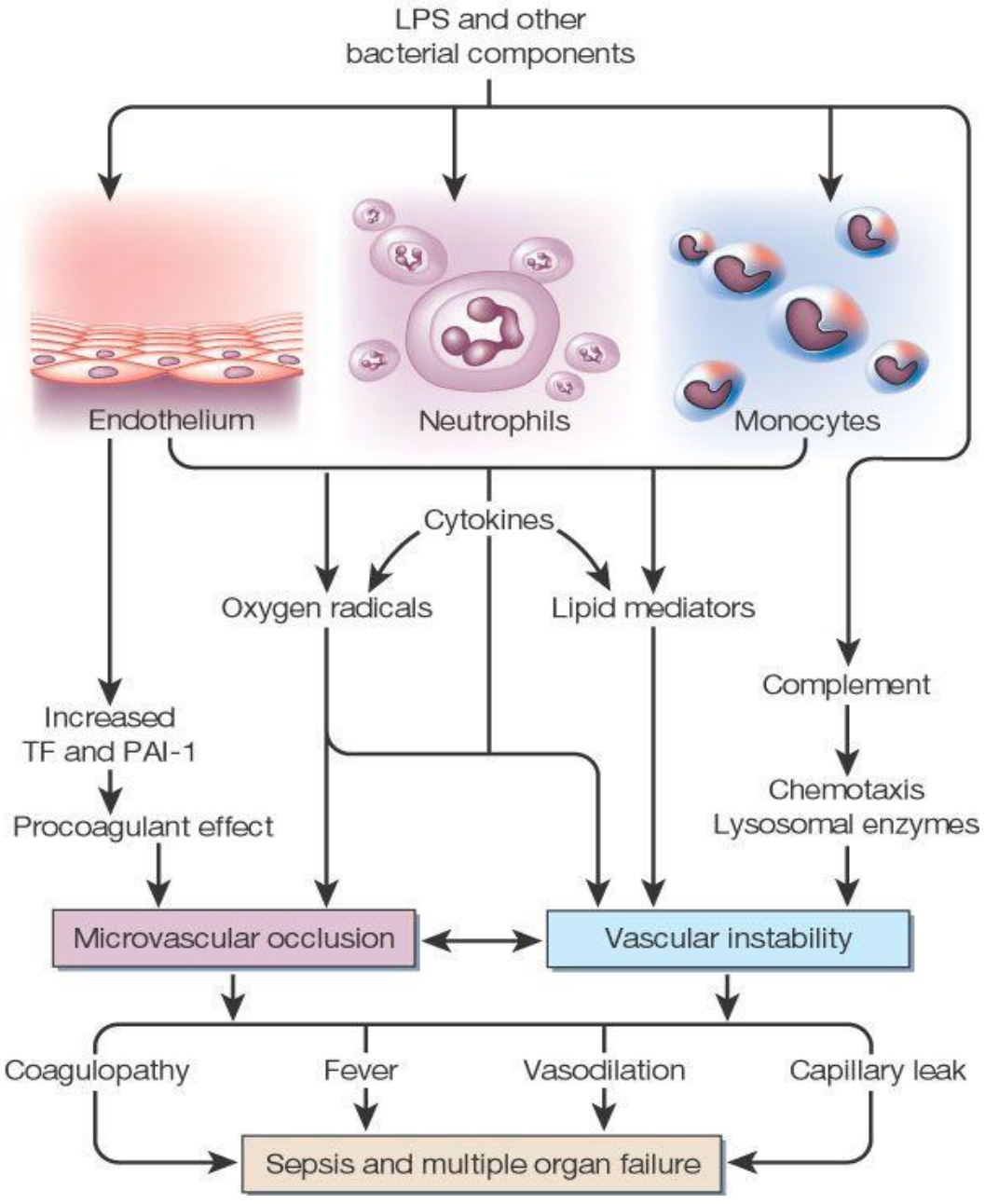
A = Apoptosis; increase in planned cell death.

O = Organ dysfunction; renal, hepatic and cardiovascular system failure.

S = Suppression of the immune system; immune paralysis (usually transitory).

The process of CHAOS take place with varying degree of severity in every infant with sepsis and correction of CHAOS, the imbalance between pro-inflammatory and anti-inflammatory cytokines ,hyper coagulation and fibrinolysis apart from killing the pathogen is required for adequate management of sepsis.[37]

PATHOGENESIS OF NEONATAL SEPSIS



DIAGNOSIS

The evaluation of tests for neonatal sepsis is important because the infection may present a very serious threat to the baby. There is an urgent need to know whether the baby has sepsis to institute treatment as quickly as possible. Confirmation of the diagnosis may take time, and diagnostic tests are used to obtain a rapid indication of the infection status. These tests are not perfect. Some real cases of infection will produce negative test results, whereas some babies without infection will test positive. The potential usefulness of the test will depend, above all, on the clinical condition of the baby. If the baby is really very sick, the test will not give very much additional information. Similarly, if the baby is evidently well, a clinical examination will be sufficient and a positive test result would not dramatically increase the probability that the baby is infected. It is in situations in which the clinical picture leaves the physician in doubt about the infection status that a diagnostic test is likely to be most useful. Thus, the result of a diagnostic test must be evaluated in the light of the clinical condition of the baby.

SEPSIS SCREEN [38,39]

All neonates suspected to have sepsis should have a septic screen to corroborate the diagnosis. However, the decision to start antibiotics need not be conditional to the sepsis screen result, if there is a strong clinical suspicion of sepsis.

A PRACTICAL SEPSIS SCREEN [40,41]

Components	Abnormal value
Total leukocyte count	<5000/mm3
Absolute Neutrophil Count	Low counts as per Manroe chart[73] for term and Mouzinho's chart[74] for VLBW infants.
Immature/total neutrophil	>0.2 %
Micro-ESR	>15 mm in 1st hour
C reactive protein (CRP)	>1 mg/dl

BLOOD CULTURE

It is the gold standard for diagnosis of septicaemia and should be performed in all cases of suspected sepsis prior to starting antibiotics.[42]A positive blood culture with sensitivity of the isolated organism is the best guide to antimicrobial therapy. Therefore it is very important to follow the proper procedure for collecting a blood culture.

The resident doctor/staff should wear sterile gloves prior to the procedure and prepare a patch of skin approximately 5 cm in diameter over the proposed veni-puncture site. This area should be cleansed thoroughly with 70% isopropyl alcohol, followed by povidone-iodine, and followed again by alcohol. Povidone-iodine should be applied in concentric circles moving outward from the centre. The skin should be allowed to dry for at least 1 minute before the sample is collected.

One-mL sample of blood should be adequate for a blood culture bottle containing 5-10 mL of culture media. Since samples collected from indwelling lines and catheters are likely to be contaminated, cultures should be collected only from a fresh veni-puncture site. All blood cultures should be observed for at least 72 hours before they are reported as sterile. It is now possible to detect bacterial growth within 12-24 hours by using improved

bacteriological techniques such as BACTEC and BACT/ALERT blood culture systems. These advanced techniques can detect bacteria at a concentration of 1-2 colony-forming unit (cfu) per mL.4

The Most Recent Diagnostic Tests of Neonatal Sepsis

Isolation of bacteria from blood is the most specific and standard method used to diagnose neonatal sepsis. The drawback of culture-based diagnosis is the 24–48 hour assay time. Newer diagnostic tests can be grouped into:

1. Acute phase reactants
2. Cell surface markers
3. Granulocyte colony-stimulating factor
4. Cytokines

1. ACUTE PHASE REACTANTS

These groups of endogenous peptides are produced by the liver as part of an immediate response to the infection or tissue injury. These reactants are C-reactive protein , procalcitonin.

C-reactive protein (CRP)

CRP is synthesized within six to eight hours of exposure to an infective process or tissue damage, with a half life of 19 hours, and can increase more than 1000-fold during an acute phase response. In a study, it was concluded that CRP, IL-6 and IgM are helpful in the early diagnosis of Gram-negative neonatal sepsis, although CRP continues to be the best single test.

A single value of C-reactive protein (CRP) has unacceptable low sensitivities, especially during the early stages of infection.[43,44]A CRP value of 5 mg/l was the best among the three

parameters with 95% sensitivity and 98% negative predictive value. The best combination was CRP ≧ 5 mg/dl and/or IgM of >or = 20 mg/dl. The use of both CRP and IgM in combination was the most helpful method in predicting Gram-negative neonatal sepsis which had a significant role in making decisions regarding antibiotic treatments.CRP values are also affected by premature rupture of membranes, maternal fever, meconium aspiration, fetal distress and the aetiology of the infection.[45,46]

Procalcitonin (PCT)

Procalcitonin which is produced by monocytes and hepatocytes, begins to rise four hours after exposure to bacterial endotoxin, reaches its peak after six to eight hours, and remains raised for at least 24 hours, with a half life of 25–30 hours. Both procalcitonin (2.3 ng/ml) and CRP (30 mg/l) had high specificity and positive predictive values (97%, 91% and 96%, 87%, respectively), though with low sensitivity (48% and 41%, respectively) for sepsis diagnosis. 70 Its overall sensitivity is 81% and specificity is 79%.[47]

The conclusion was that procalcitonin >2.3 ng/ml or CRP > 30 mg/l indicates a high likelihood for neonatal sepsis, and antibiotic therapy should be continued even in the presence of sterile cultures. However, it is not a readily available diagnostic assay in most institutions .

2. CELL SURFACE MARKERS

Neutrophil CD11b and CD64 appear to be promising markers for the diagnosis of early- and late-onset infections. For culture-positive sepsis episodes, the CD64 index had the highest area under the curve (0.852) of all haematological variables, with a sensitivity of 80% and a specificity of 79%, and a cutoff value of 4.02. Therefore, neutrophil CD64 is a highly sensitive marker for neonatal sepsis. Prospective studies incorporating CD64 into a sepsis scoring system are warranted

3. GRANULOCYTE COLONY-STIMULATING FACTOR

Granulocyte colony-stimulating factor (GCSF), a mediator produced by bone marrow, facilitates proliferation and differentiation of neutrophils, and has been proposed to be a reliable infection marker for early diagnosis of neonatal sepsis. A concentration ≥ 200 pg/ml has a high sensitivity (95%), and negative predictive value (99%) for predicting early onset neonatal bacterial and fungal infections

4. CYTOKINES

As antigen-specific immunity develops later in infant's life, e.g. at 2 years of age in case of encapsulated bacteria, neonates initially depend on their natural (innate) immunity. This includes phagocytes (by monocytes, tissue macrophages, and neutrophils), natural killer cells, and humeral mediators (CRP, complements, transp- lacentally- acquired maternal antibodies). In response to antigens such as bacterial endotoxins, activated tissue macrophages produce tumour necrosis factors (TNF) and interleukins (IL). These proinflammatory cytokines stimulate endothelial cells to express receptors for intercellular adhesion molecules on white blood cells. This initiates the cytokine cascade towards the increased production of IL6, IL8, and chemokine's. Newborn infants display a higher percentage of IL6 and IL8 positive cells than adults do. There is a sharp rise in IL6 concentration on exposure to bacterial products, which precedes the increase in CRP. Umbilical cord blood IL6 has consistently been shown to be a sensitive marker for diagnosing early-onset neonatal sepsis at the onset of infection, compared with other biochemical markers, including CRP, IL1ß, TNFα, and Eselectin, although sensitivity is reduced at 24 and 48 hours, since IL6 concentrations fall rapidly and become undetectable after 24 hours. The measurement of IL6 (early and sensitive) along with CRP (late and specific) in the first 48 hours of presumed septic episodes, improves the sensitivity compared with either of them alone .

LABORATORY TESTS

1. Lumbar puncture

A lumbar puncture (LP) should be considered in all neonates for whom blood culture evaluation for sepsis is performed, because clinical signs suggesting meningitis can be lacking in young infants.

In a retrospective study of all neonates born in United States army hospitals from 1988 to 1992, 8 of the 36 term infants with meningitis had no symptoms referable to the central nervous system, and had sterile blood cultures .[48]In addition, three infants with both positive cerebrospinal fluid (CSF) and blood cultures were asymptomatic.

In our practice, we always perform a LP for symptomatic term infants. For asymptomatic term infants, meningeal doses of Ampicillin and Gentamicin in combination are initiated after evaluation that includes a blood culture. The CSF should be sent for culture, gram stain, cell count, and protein and glucose concentration to determine whether the infant has meningitis.

2. Urine and other potential infected sites

Urine culture obtained by catheter or bladder tap should be included in the sepsis evaluation for infants >6 days of age. A urine culture need not be routinely performed in the evaluation of an infant ≤6 days of age, because a positive urine culture in this setting is a reflection of high-grade bacteraemia rather than an isolated urinary tract infection.

3. Chest radiography

It should be obtained in an infant with respiratory distress. Localized infiltrates may be due to pneumonia. Cultures should also be obtained from any other potential foci of infection (eg : purulent eye drainage or pustules).

CRITERIA FOR THE DIAGNOSIS OF NEONATAL SEPSIS [49]

Clinical Variables

- Temperature instability
- Heart rate _180 beats/min or _100 beats/min
- Respiratory rate >60 breaths/min plus grunting or desaturations
- Lethargy/altered mental status
- Glucose intolerance (plasma glucose >10 mmol/l)
- Feed intolerance

Hemodynamic variables

- Blood pressure 2 SD below normal for age
- Systolic pressure <50mm Hg (newborn day 1)
- Systolic pressure <65mm Hg (infants _ 1 month)

Tissue perfusion variables

- Capillary refill >3 s
- Plasma lactate >3 mmol/l

Inflammatory variables

- Leukocytosis (WBC count >34 000_109/l)
- Leukopenia (WBC count <5000_109/l)
- Immature neutrophils >10%
- Immature:Total neutrophil ratio >0.2
- Thrombocytopenia <100 000_109/l
- CRP >10 mg/l or 2 SD above normal value
- Procalcitonin >8.1 mg/dl or 2 SD above normal value
- IL-6 or IL-8>70 pg/ml
- 16S PCR positive

Interpretation

- Proven Sepsis: A positive blood culture or PCR in the presence of clinical signs and symptoms of infection. For CoNS two positive blood cultures or one positive blood culture plus a positive CRP.
- Probable Sepsis: Presence of signs and symptoms of infection and at least two abnormal laboratory results when blood culture is negative.
- Possible Sepsis: Presence of clinical signs and symptoms of infection plus raised CRP or IL-6/IL-8 level when blood culture is negative

MANAGEMENT

1. SUPPORTIVE CARE

Attention should be given to basic supportive care in a sick child.[50]He/she should be nursed in a thermo-neutral environment taking care to avoid hypo/hyperthermia. Oxygen saturation should be maintained in the normal range; mechanical ventilation may have to be initiated if necessary. If the infant is hemodynamically unstable, intravenous fluids should be administered and the infant is to be monitored for hypo/hyperglycemia. Volume expansion with crystalloids/colloids and judicious use of inotropes are essential to maintain normal tissue perfusion and blood pressure. Packed red cells and fresh frozen plasma might have to be used in the event of anaemia or bleeding diathesis.

- **Thermal care**: Thermo-neutral environment should be ensured
- **Respiratory:**Adequate oxygenation with blood gas monitoring, and initial oxygen therapy or ventilator support (if needed) must be ensured.
- **Cardiovascular**: Blood pressure and perfusion must be supported to prevent shock. Volume expanders like normal saline, and inotropes such as dopamine or dobutamine may be needed. Intake and output of fluids should be monitored.
- **Hematologic:** DIC and neutropenia should be treated as per standard protocol

- **CNS:** Seizures and SIADH should be addressed with proper attention.
- **Metabolic**:Hypoglycemia, hyperglycemia and metabolic acidosis should monitor and treated regularly

2. ANTIMICROBIAL THERAPY

There cannot be single recommendations for the antibiotic regimen for neonatal sepsis in all settings. The choice of antibiotics depends on the prevailing flora responsible for sepsis in the given unit and their antimicrobial sensitivity. The initial choice of drugs for empirical treatment is dependent on knowledge of the probable pathogens based on the perinatal history, including any maternal symptoms, cultures, or instrumentation.[51] Decision to start antibiotics is based upon clinical features and/ or a positive septic screen. However duration of antibiotic therapy is dependent upon the presence of a positive blood culture.

DURATION OF ANTI-BIOTIC THERAPY IN NEONATAL SEPSIS

Diagnosis	**Duration**
Meningitis (with or without positive blood/CSF culture)	21 DAYS
Blood culture positive but no meningitis	14 DAYS
Culture **negative** sepsi**s (screen positive** and clinical course **consistent with sepsis)**	5 TO 7 DAYS

Indications for Starting Antibiotics

The indications for starting antibiotics in neonates at risk of EOS include any one of the following:

(a) Presence of >3 risk factors for early onset sepsis

(b) Presence of foul smelling liquor

(c) Presence of ≥2 antenatal risk factor(s) anda positive septic screen

(d) Strong clinical suspicion of sepsis.

The Indications For Starting Anti-Biotics In LOS Include:

(a) Positive septic screen and/or

(b) Strong clinical suspicion of sepsis. [52]

Prophylactic antibiotics: We do not use prophylactic antibiotics in the following circumstances: infants on IV fluids/TPN, meconium aspiration syndrome, and after exchange transfusion(s). An exchange transfusion conducted under strict asepsis (single use catheter, sterile gloves, removal of catheter after the procedure) does not increase the risk of sepsis and hence does not merit antibiotics. However a messy exchange transfusion could be treated with prophylactic antibiotics. In our unit, ventilated neonates are treated with prophylactic amikacin for the period of ventilation.

Choice of antibiotics: Empirical anti-biotic therapy should be unit-specific and determined by the prevalent spectrum of etiological agents and their anti-biotic sensitivity pattern. Antibiotics once started should be modified according to the sensitivity reports.[53] Immunotherapy used as an adjuvant for the prevention and treatment of neonatal sepsis holds promise.

EMPIRICAL CHOICE OF ANTI-BIOTICS FOR TREATMENT OF NEONATAL SEPSIS[54]

Clinical situation	Clinical situation	Meningitis
FIRST LINE Community-acquired and (Resistant strains unlikely)	Penicillin or Ampicillin and Gentamicin	Add Cefotaxime
SECOND LINE Hospital-acquired and Some strains are likely to be resistant	Ampicillin or Cloxacillin Gentamicin or Amikacin	Add Cefotaxime
THIRD LINE Hospital-acquired sepsis and (Most strains are Amikacin; Likely to be resistant)	Cefotaxime or Piperacillin-Tazobactam or Ciprofloxacin	Same (Avoid Cipro)

The empirical choice of anti-biotics is dependent upon the probable source of infection. For infections that are likely to be community-acquired where resistant strains are unlikely, a combination of ampicillin or penicillin with gentamicin may be a good choice as a first line therapy.

For infections that are acquired during hospital stay, resistant pathogens are likely and a combination of ampicillin or Cloxacillin with gentamicin or amikacin may be instituted. In nurseries where this combination is ineffective due to the presence of multiple resistant strains of Klebsiella and other gram-negative bacilli, a combination of a third generation cephalosporin (Cefotaxime or ceftazidime) with amikacin may be appropriate. Third

generation Cephalosporins have very good CSF penetration and are traditionally thought to have excellent anti-microbial activity against gram negative organisms. Hence they were considered to be a good choice for the treatment of nosocomial infections and meningitis. However, recent reports suggest that at least 60-70% of the Gram-ve organisms are resistant to them.

More over, routine use of these anti-biotics might increase the risk of infections with ESBL (extended spectrum beta-lactamase) positive organisms. Therefore it is preferable to use anti-biotics such as Piperacillin-Tazobactam or Methicillin/Vancomycin in units with high incidence of resistant strains. A combination of Piperacillin-Tazobactam with amikacin should be considered if pseudomonas sepsis is suspected. Penicillin resistant staphylococcus aureus should be treated with Cloxacillin, Nafcillin or Methicillin. Addition of an amino glycoside is useful in therapy against staphylococcus. Methicillin resistant staphylococcus aureus (MRSA) should be treated with a combination of ciprofloxacin or Vancomycin with amikacin. Ciprofloxacin has excellent activity against gram-negative organisms also; however, it does not have good CSF penetration. It may be used for the treatment of resistant gram-negative bacteremia after excluding meningitis. For sepsis due to enterococcus, a combination of ampicillin and gentamicin is a good choice for initial therapy. Vancomycin should be used for the treatment of enterococcus resistant to the first line of therapy. The dosage, route, and frequency of commonly used anti-biotics are given in Table

Reserve anti-biotics: Newer anti-biotics like Aztreonam, Meropenem and Imipenem are also now available in the market. Aztreonam has excellent activity against gram-negative organisms while Meropenem is effective against most bacterial pathogens except Methicillin resistant staphylococcus aureus (MRSA) and enterococcus. Imipenem is generally avoided in neonates because of the reported increase in the incidence of seizures following its use.

Empirical use of these anti-biotics should be avoided; they should be reserved for situations where sensitivity of the isolated organism warrants its use.

3.ADJUNCTIVE THERAPY

Exchange transfusion (ET): Sadana***et al.,*** have evaluated the role of double volume exchange transfusion in septic neonates with sclerema and demonstrated a 50% reduction in sepsis related mortality in the treated group. We perform double-volume exchange transfusion with cross-matched fresh whole blood as adjunctive therapy in septic neonates with sclerema.[55]

LITERATURE REVIEW

Christoph *et al*, (2012)havemeasured of the CBCin early-Onset Neonatal Sepsis in USA. Their result was Low white blood cell counts, low absolute neutrophil counts, and high immature-to-total neutrophil ratios which is associated with increasing odds of infection (highest odds ratios: 5.38, 6.84, and 7.97, respectively). Specificity and negative predictive values were high (73.7–99.9% and >99.8%). However, sensitivities were low (0.3–54.5%) for all complete blood cell count indices analyzed..Low white blood cell count, absolute neutrophil count, and high immature-to-total neutrophil ratio were associated with increasing odds of infection, but no complete blood cell count-derived index possesses the sensitivity to rule out reliably early-onset sepsis in neonates[56].

Farhat *et al*(2014) have a study of Clinical Manifestation and Laboratory Findings of Positive Blood Culture in Iran .They collected 100 records of positive blood culture in the neonates suffering from septicemia. . Their result was in one hundred septicemic neonates who had been admitted in the NICU were included in the study (57 male 43 female). There were 72 pre-term cases and 28 term neonates. Low birth weight (LBW) was observed in 75 cases while others were normal. Forty-four subjects had been born via natural vaginal delivery and 56 cases were born via Cesarean section. Moreover, 67 neonates were admitted within the first 24 hours of birth and 31 cases had a normal ESR . The hemoglobin level was normal in 58 cases, while it declined in 42 neonates. WBC was normal in 85 cases, while it saw an increase and decrease in 11 and 4 cases, respectively[57].

Khair and kheir *et al*, (2014) have a study in the Prevalence and outcome in a tertiary neonatal unit in Sudan , thirty five (56.5%) of maternal delivery were delivered by emergency caesarean section , forty six (74.2%) of patients mothers did not have prolonged rupture of membranes (PROM), Four (6.5%)had ruptured their membranes for less than 24 h and twelve (19.4%) experienced it for more than 24, twenty four (38.7%) of mothers had a history of diseases, of which UTI was found to be the most common[58].

Edward *et al*(2015) have a study of Diagnosis of Neonatal Bacterial Infection: Hematologic and Pathologic Findings in Fatal and Nonfatal Cases in Denver One hundred infants hospitalized between 1970 and 1979 received a sepsis work-up, died within 72 hours, and then had a complete autopsy. Abnormalities of the WBC's, NC, and PC with a trend toward leukopenia and neutropenia. In contrast, nonfatal cases of bacterial infection often

demonstrated an increase in BC and NC. Although a trend toward multiple CBC abnormalities in infected (and especially fatally infected) patients was noted, some infected patients had no abnormalities and some seriously ill non infected patients had multiple CBC abnormalities. In all, 80% of the infected newborns studied had abnormal pre mortem hematologic counts. one of the 23 non infected infants (P value <.001). Megakaryocytopenia developed in four of 23 patients with fatal infection but none of the controls(P < .001)[59].

Haque SM., *et al.*, conducted a study on Identification of bacterial isolates in neonatal sepsis and their antimicrobial susceptibility. This cross-sectional descriptive study was conducted to determine the pattern of bacterial agents causing neonatal sepsis and their susceptibility pattern to various antimicrobial agents. Out of 1000 screened blood cultures, 87(8.7%) reported as positive and the gram positive and gram negative bacteria accounted for 21(24.1%) and 66(75.9%) respectively. The most common gram positive organisms were *Coagulase Negative Staphylococcus Aureus* (CONS) (18.4%) and *Staphylococcus Aureus* (4.6%) and gram negative organisms were *Acinetobacter* (34.4%), *Pseudomonas* (21.8%) and *Klebsiella spp.* (6.9%). The susceptibilities were remarkably low to Ampicillin (20%) and Cefotaxim (29.6%) for both gram positive & gram negative isolates. Gram positive group had susceptibilities of 71.1% to Gentamicin, 85.7% to Imipenem & 100% to Amikacin & Vancomycin. Gram negative isolates showed higher sensitivities to Colistin (96.9%), Piperacillin-Tazobactum (78.7%), Imipenem (74.2%), and Levofloxacillin (71.2%), respectively. Gram-negative bacteria showed high level of resistance to commonly used antibiotics (Ampicillin, Ceftazidime and Cefotaxim). Gentamicin, Amikacin, Imipenem and Levofloxacin were the most effective drugs compared to others[60].

Rajlakshmi Viswanathan., *et al.*, conducted a study on aetiology and antimicrobial resistance of neonatal sepsis at a tertiary care centre in Eastern India. The study was done to review aetiological agents of neonatal sepsis and their antibiotic resistance pattern over the past 3 years. The incidence of culture proven neonatal sepsis among inborn babies was 14.8/1,000 live births. The proportion of culture positive sepsis for outborn babies admitted in neonatal intensive care unit was 8.3%. Gram negative aetiology was predominant (71.6%), with *Klebsiella pneumoniae* being the most common isolate. Non fermenting Gram negative bacilli like *Acinetobacter sp* emerged as an important cause of infection. The etiology of early onset and late onset sepsis was similar. The proportion of resistance to common first and second line antibiotics like Ampicillin (98.5%), Gentamicin (84.4%), Amikacin (65.6%) and Cefotaxime (81.3%) was high[61].

Shahla Afsharpaiman *et* al,(2003). A historical cohort study was conducted on 84 patients with neonatal sepsis who were admitted to the neonatal intensive care unit (NICU) wards of Baqiyatallah and Najmieh University hospitals in Tehran, between 2003 and 2006. Clinical, demographic and laboratory data was collected from medical records.Among all the comprised neonates, 44 patients were diagnosed with early-onset sepsis, 23 cases with late-onset sepsis and others with nosocomial sepsis. The most common isolated pathogen in all groups was *Enterobacter*, and was responsible for 31.4%, 47.8% and 41.2% of the episodes of sepsis, according to the sepsis type mentioned above, respectively. Susceptibility of common sepsis related pathogens to imipenem and gentamycin gradually reduced over the years between 2003 and 2006. Total mortality and morbidity rates due to neonatal sepsis were estimated at 27.4% and 89.3%, respectively. Mortality following sepsis was found more in boys (Odds Ratio (OR)=4.897, Conifdence Interval (CI)=95%, *P*=0.031), and those with low birth weight (OR=4.406, CI: 95%, *P*=0.011). Higher sepsis related co-morbidity was found in neonates following cesarean delivery (OR=6.280, CI: 95%, *P*=0.025)[62].

Chen CY *et* al,(2006). A total of 109 episodes of sepsis were identified in 100 neonates. The incidence of sepsis was 4.06% among all NICU admissions. Most neonates with early-onset sepsis were term infants, while very low birth weight (VLBW) and preterm infants accounted for the majority of cases of late-onset sepsis. In early-onset sepsis, the most common pathogens responsible included group B streptococci (GBS) (36%) and Escherichia coli (E. coli) (26%). GBS was associated with more meningitis involvement but lower incidence of mortality compared with E. coli. The most common causative microorganisms in late-onset sepsis were coagulase-negative staphylococci (CONS) (40%) and Candida (15%). The sepsis-related mortality rates were higher in early-onset sepsis (10%) than in late-onset sepsis (7%).

Unlike previous reports from Taiwan, in the present study, GBS was found to be the leading pathogen in early-onset sepsis. GBS screening and intrapartum antibiotic prophylaxis guidelines should be used in Taiwan to prevent early neonatal sepsis. The most common causative microorganisms of late-onset sepsis were CONS and Candida species. Candida parapsilosis was associated with a high mortality rate[63].

Saleem AF *et* al, (2011). During the period 2006-2011, 104 of 2768 neonates developed late-onset K. pneumoniae sepsis. The overall incidence of late-onset K. pneumoniae sepsis was 3.7% (37/1000 NICU admissions), with the highest annual incidence being 53/1000 in 2010. Most cases were males (n = 64; 62%) and most were premature and very low birth weight (n = 68; 65%). More than 80% of isolates were resistant to ampicillin + clavulanic acid, gentamicin, aztreonam, and cephalosporins. An increasing trend of resistance to amikacin, fluoroquinolones, piperacillin/tazobactam, and imipenem was observed. In 2011, three-quarters (72%; n=13) of late-onset K. pneumoniae were CR K. pneumoniae. Seventeen (16%) neonates died. Being male (p = 0.06, adjusted odds ratio (AOR) 9.2, 95% confidence interval (CI) 1.3-66.9), having an extremely low birth weight (p = 0.01, AOR 6.1, 95% CI 0.8-44.4), having severe thrombocytopenia (p = 0.07, AOR 3.9, 95% CI 1.2-13.0), and failure to achieve microbiological clearance (p < 0.001, AOR 19.6, 95% CI 4.0-98.0) were significantly associated with mortality due to late-onset K. pneumoniae sepsis[64].

Yilmas N.O *et*,al, (2010). One hundred and forty-seven and 227 neonates had been diagnosed as late-onset sepsis in 2004 and 2008, respectively. Coagulase-negative staphylococcus was the most frequent microorganisms. Gram-negative bacilli, particularly Pseudomonas aeruginosa showed a significant increase in years. The mortality rate was 11.5% and 19% in 2004 and 2008, respectively. Birth weight, gestational age, and infection with Klebsiella spp. isolates were found to have significant association with sepsis mortality in our neonatal intensive care unit (NICU)[65].

The present study emphasizes the importance of periodic surveys of sepsis encountered in particular neonatal setting to recognize the trend. Increased Gram-negative bacilli rate was possibly related to the widespread use of antibiotics in our NICU[66].

Sindhu Sivanandhan., *et al.*, studied a review article namely choice and duration of anti-microbial therapy for neonatal sepsis and meningitis. This review aims to examine the appropriate choice of empiric anti-microbial agents and optimal duration of therapy in neonates with suspected sepsis, culture proven sepsis and meningitis. They concluded that the choice of anti-biotic should be based on the causative organism and the pattern of anti-biotic susceptibility. The combination of ampicillin and gentamicin is an appropriate choice for empirical therapy of neonatal EOS in developed countries where *GBS* and *E.coli* continue to be the predominant organism. For LOS, starting cloxacillin and gentamicin may be appropriate in a stable neonate[67].

Sharma C,M *et* al,(2013). His prospective study was carried out at a medical college during the period from 1st April 2011 to 31st March 2013. A total of 364 cases of suspected sepsis were admitted in our NICU during the mentioned period. Out of which, 137 cases were positive for culture. All the neonates of suspected sepsis were screened by using a panel consisting of CRP, ANC, I/T ratio, micro ESR and culture and sensitivity.

A total of 137 cultures were found to be positive out of 364 cases. The most common organism isolated was Staphylococcus aureus (37.22%) followed by Klebsiella pneumoniae (27.01%) and Escherichia coli (19.70%). Other organisms were much less in number, which included pathogenic Streptococci, Coagulase negative Staphylococci (CoNS), Pseudomonas, Acinetobacter and Enterobacter species. The gram positive organisms except Streptococci displayed a high degree of resistance to most penicillins and ciprofloxacin but were sensitive to vancomycin, amikacin and cefepime. There was a high incidence of resistance noted with ampicillin, gentamicin and ciprofloxacin amongst most gram negative organisms' where-in cefepime, amikacin and meropenem were effective in most cases[68].

Ozkan H *et* al, (2013). A total of 151 preterm infants with culture-proven neonatal sepsis were enrolled in this prospective study. The infants were classified into three groups with regard to the onset of sepsis: early onset sepsis (EOS), late-onset sepsis (LOS) and very late-onset sepsis (VLOS). A sepsis screen including whole blood count, blood smear, infection markers and cultures was performed before initiating antibiotic therapy.

EOS, LOS and VLOS groups consisted of 23, 86 and 42 infants, respectively. Coagulase-negative staphylococci (CONS) was the most common organism in all sepsis groups. The main factors associated with EOS included presence of premature rupture of membranes, antibiotic use in pregnancy and choriamnionitis. Previous antibiotic use was the main factor associated with LOS, while low birthweight was the main factor in infants with VLOS. Although mortality rate due to Gram-negative bacteria and fungi was higher, CONS was an important cause of mortality in infants with LOS and VLOS[69].

Hervas J. A *et* al,(2001). There were 513 cases of culture-proved sepsis and/or meningitis in neonates. In late onset infections Klebsiella pneumoniae and Staphylococcus epidermidis were the most frequent isolates in the period 1977 through 1991. Enterobacter was the most common isolate in the period 1992 through 1998. During this latter period Candida infections also increased, and the resistance rate of Enterobacter to cefotaxime was higher (59.2%). Decrease in early onset infections and increase in late onsets (4.6/1,000 live

births) were observed in the second period. From 1977 to 1998, 45 episodes of sepsis and/or meningitis by Enterobacter species were identified in 44 patients (8.7% of all neonatal bacteremias). Three patients with Enterobacter bacteremia died (6.6%, 0.03/1,000 live births). During 1995 through 1997 5 different clones causing sepsis were identified and 3 were predominant. In 1997 there was an outbreak of Enterobacter disease. After cleaning, cohort nursing and hygiene reinforcement, Enterobacter was not isolated in the next 2 years. No change in the antibiotic policy was made[70].

ShreshtaH et al,(2013). The stdy wasc onducted on Bacterial isolates and its antibotic susceptibility pattern in NICU. The blood culture yield by conventional method was 44.13% with nosocomial sepsis accounting for 10.79%. 84.08% were culture proven early onset sepsis and 15.95% were late onset sepsis. Klebsiella infection was the commonest organism isolated in early, late and nosocomial sepsis but statistically not significant. Gram positive organisms were 39.36% in which Staphylococcus aureus was the leading microorganism followed by coagulase negative staphylococcus areus. Gram negative organisms were 60.64% amongst them Klebsiella was the most often encountered followed by Pseudomonas. The most common organism Klebsiella was 87.5% and 78.3% resistance to ampicillin and gentamycin respectively. Among gram negative isolates 87.5% and 77.2% were resistance to ampicillin and gentamycin respectively. Among gram positive isolates 58.5% and 31.5% resistance were noted to ampicillin and gentamycin respectively. Resistance to cefotaxim to gram negative and gram positive isolates were 87.34% and 59.35% respectively. [71].

Jnkovic B *et* al,(2001). The study was conducted on C-reactive protein concentrations during initial (empiric) treatment of neonatal sepsis.
A total of 1520 neonates were evaluated during this study period and 47 patients fulfilled criteria for final analysis. In 14 of 47 patients initial antibiotic treatment was inappropriate. The most frequent resistant strains was KI. pneumoniae (6) followed with St. aureus (4), E. coli (2) and Pseudomonas (2). During initial evaluation six patients had concomitant meningitis while two had concomitant septic arthritis and two necrotizing enterocolitis, respectively. Seven (50%) of 14 patients with non-adequate initial treatment died. In 33 cases of adequately treated septicaemia the course was uncomplicated and no lethal outcome was observed. In the first group of 14 patients who received inappropriate treatment serum CRP concentations (mg/L; mean and +/- SD) were: CRP0 = 107.5 +/- 65.6; CRP1 = 155.3 +/- 75.7; CRP2 = 209.1 +/- 67.0, while in 33 repeated samples of the 33 patients in the second

group who received adequate treatment the following results were recorded: CRP0 = 124.0 +/- 78.1; CRP1 = 133.8 +/- 63.5; CRP2 = 94.6 +/- 46.4. Increase in serum CRP concentration in the first group during the first 48 hours of initial non-adequate therapy was significantly higher (p = 0.015, two way ANOVA) than in the second group with appropriate treatment.

During the first 24 hours of treatment increase in serum concentration of CRP was registered in 12 (85.7%) of 14 measurements in patients with non-adequate therapy and in 19 (56.7%) of 33 measurements in patients with adequate therapy. In the first group during the second day of treatment, in 11 (78.6%) of 14 cases an increase in serum CRP concentration was recorded while in 3 (14.3%) cases CRP concentration decreased. In 31 (91.2%) of 34 measurements in patients with adequate treatment CRP concentration decreased during the second day of treatment and in only 3 (8.8%) cases CRP concentration increased. With an increase in serum concentration of CRP more than 10 mg/L in the second day of antibiotic treatment, probability of non-adequate antibiotic therapy (positive predictive value) was estimated to be 77.0%. Any recorded decrease of serum CRP concentration may confirm appropriate choice of antibiotics during the second day of treatment with probability of 93.3% (negative predictive value). [72].

Kayange N *et* al, (2010). The sudy was conducted on Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza-Tanzania**. [73]**

Among 770 neonates admitted during the study period; 300 (38.9%) neonates were diagnosed to have neonatal sepsis by WHO criteria. Of 300 neonates with clinical neonatal sepsis 121(40%) and 179(60%) had early and late onset sepsis respectively. Positive blood culture was found in 57 (47.1%) and 92 (51.4%) among neonates with early and late onset neonatal sepsis respectively (p = 0.466). Predictors of positive blood culture in both early and late onset neonatal sepsis were inability to feed, lethargy, cyanosis, meconium stained liquor, premature rupture of the membrane and convulsion. About 49% of gram negatives isolates were resistant to third generation cephalosporins and 28% of Staphylococcus aureus were found to be Methicillin resistant Staphylococcus aureus (MRSA). Deaths occurred in 57 (19%) of neonates. Factors that predicted deaths were positive blood culture (p = 0.0001), gram negative sepsis (p = 0.0001) and infection with ESBL (p = 0.008) or MRSA (p = 0.008) isolates.

Our findings suggest that lethargy, convulsion, inability to feed, cyanosis, PROM and meconium stained liquor are significantly associated with positive blood culture in both early and late onset disease. Mortality and morbidity on neonatal sepsis is high at our setting and is significantly contributed by positive blood culture with multi-resistant gram negative bacteria.

Lee N.C *et* al, (2004). The study was conducted on Neonatal bacteremia in a neonatal intensive care unit: analysis of causative organisms and antimicrobial susceptibility. Totally, 754 blood cultures were done on 623 patients. Fifty-eight patients experienced 85 episodes of bacteremia, with 87 isolates cultured. The incidence of bacteremia in our NICU was 9.31% (58/623) with an incidence density of 10.98/1000 patient-days. The overall mortality rate was 7.22%. The case fatality rate of bacteremia was 20.7% (12/58). The bacterial pathogens encountered, in order of frequency, were coagulase-negative Staphylococcus (29%), Staphylococcus aureus (22%), and Enterobacter cloacae (17%). All of the gram-positive bacteria were susceptible to vancomycin, while the gram-negative bacteria were susceptible to imipenem, amikacin and ciprofloxacin. Oxacillin-resistant S. epidermidis, oxacillin-resistant S. aureus, and multi-drug resistant enterobacteriae were the leading microorganisms causing bacteremia in our NICU.

It is an endless struggle to combat neonatal infection. Periodic evaluation of bacterial antibiotic susceptibility is necessary. More judicious selection of antibiotics and rotating antibiotic regimens should be kept in mind to reduce the resurgence of multidrug resistant strains. [74]

Kumar M D.*, et al.,* studied the anti-microbial utilization and cost pattern on babies with neonatal sepsis. In this prospective study, the two initial anti-microbial regimens which were commonly preferred were ampicillin with amikacin and a combination of Piperacillin plus Tazobactam and amikacin. Treatment of gram negative sepsis and LOS was comparatively more expensive. Hence early diagnosis and appropriate anti-bacterial therapy could prevent the monetary burden of this dreadful disease. [75]

Tsehaynesh Geyesus.*, et al.*, done a study on bacterial etiologic agents causing neonatal sepsis and associated risk factors in Gondar, Northwest Ethiopia. This cross- sectional study was conducted among neonates suspected to sepsis which aimed to identify bacterial etiologic agents, their anti-microbial susceptibility pattern and associated risk factors of

neonatal sepsis among neonates. The study concluded that the isolation rate of bacterial pathogens in neonatal sepsis was considerably high. In addition, nearly 70% of isolates were MDR strains. Low birth weight, low Apgar score, preterm delivery and caesarian section modes of delivery were associated risk factors. Therefore, appropriate antenatal care follow up, and health education should be encouraged, especially on the importance of natural way of delivery. [76]

NEED OF STUDY

The world health organization (WHO) estimates that more than 4 million neonates die each year. In 1995 neonatal deaths are 5 million; the numbers of neonatal deaths are decrease to 4 million in 2005,but 98% still occurred in the less developed countries among them Infection was the main cause.

The present figure of 40per 1000 live births in India is too high .neonatal morbidity was found to be 56.8% and 37.3% amongst slum and non-slum that severe neonatal illness were higher among slum as compared to non-slum areas.

Neonatal morbidity distribution among the non-slum areas in luknow was respiratory illness (12%), skin problems (12%), eye infections (4%) and neonatal sepsis (0%). Five neonates from slums were taken to quacks out of which four had very severe disease symptoms. Two of these neonates subsequently died with in 4-6 weeks of life, one due to probable meningitis and the other due to neonatal sepsis.

Current status of neonatal health services in India is dis-organized recently only 20 of the 125 medical colleges in the country have special care neonatal units. A series of services of neonatal centers conducted in the country revealed that out of 28 units only 50% had satisfactory resuscitation facilities while 33% had inadequate.

Major causes of death in neonates in India were due to respiratory dis-orders, GI disturbances and injuries, chickengunya. More than 1.25 million suspected cases have been reported and (752245) were from Karnataka state, Maharastra (258998) and also affected states were Andhra Pradesh, Madhya Pradesh, Tamilnadu and Gujarat.

A study in Australia the risk of death from pneumonia in child hood is in the neonatal period. It is estimated that pneumonia contributes to between 750000- 1.2 million neonate's deaths annually according for 10% of global child mortality.

Study was shown that the incidence of neonatal herpes simplex virus infections were identified 35 confirmed cases of herpes simplex virus and incidence was (12.9%) per 1,00,000 live births in Atlanta Georqia, USA.

In adequate postnatal counseling to mothers on neonatal care including neonatal danger signs was observed. The potent risk factors for neonatal infection were the number of siblings and baby care at post-natal care facilities. A resent study focused on the duration of exclusive breast feeding necessary to protection against infection during infancy.

Separation of new borns from young siblings to prevent neonatal infection needs to be emphasized to mothers. Furthermore can found new risk factors post-natal care facilities and home aides to decrease the incidence of neonatal infection, standards of hygiene for post -natal care facilities need to be established for the prevention of infections in neonates.

When women's acquired the knowledge prior to or during pregnancy. One to prevent infection is through simple hygiene practices, such hand washing and particularly adapts the hygienic behavior to prevent also heard about it from a doctor, hospitals, clinics and other professionals 29%. The awareness of women's knowledge on hand washing, not sharing drinking glass and not kissing young children on the mouth appeared to be generally acceptable. These are the preventable practices give the awareness to the mothers to prevent the neonatal infection.

Based on the review of literature and the personal experience of the investigator during hospital visits was found that many neonates affected with neonatal infections and there was less awareness and practices on prevention of neonatal infections.

Hence the investigator felt the need to assess the knowledge on prevention of neonatal infections, with a view to prepare structure teaching programme which will be useful for the mothers for prevention of neonatal infections.

AIM AND OBJECTIVES

AIM

To study the Retrospective assessment of Neonatal sepsis cases in Government hospital Tirupur.

OBJECTIVES

1. To find out the drug utilization pattern for Neonatal sepsis patients in a secondary care hospital.
2. To assess the risk factors associated with Neonatal sepsis.
3. To study the effectiveness of antibiotics.
4. To assess the therapeutic aspects of drugs.
5. To encourage rational prescribing**.**

PLAN OF WORK

- Initial study to identify the scope of work
- Literature survey
- Preparation of study of protocol
- Obtaining consent from the hospital authority
- Collection of data format from case sheets
- Data analysis
- Evaluations of data
- Results and Discussion
- Summary & Conclusion

METHODOLOGY

Study site: The study is conducted in Government district headquarters hospital, Thirupur district, Tamil Nadu.

Study period: September 2017 - Februvary 2018

Study type: Retrospective study

Sample size: 80 patients

Study population: babes attended in neonatal intensive care unit and case sheets from medical record department.

Inclusion criteria:

- New babies diagnosed with neonatal sepsis
- Patients those willing to give their consent.

Exclusion criteria

- Babies with age over 4 weeks
- Adults

Study procedure

The present study was conducted at Government district headquarters hospital, Thirupur for the retrospective assessment of Neonatal sepsis cases The study involves mainly 3 steps.

1-Collection of the prescriptions

The prescription were collected from the Neonatal intensive care unit and medical record department of Government district headquarters hospital, Thirupur. For a period of 6 months that is from Sep 2017 to Feb 2018

The study was conducted in retrospective manner, The data was collected from the respective departments of the hospital on proforma.

2-Analysing the prescription

The Collected data from the prescription were entered in to proforma were analysed. The pattern of drug use and duration of therapy, mostly prescribed drugs are noted and other important parameters are noted.

3-Statistical analysis

The datas were collected according to the proforma and was entered in separate excel sheets in respective of their proformas or the parameters and they were analysed for the outcomes of the individual parameters like gender, age groups, others by making a table first and then followed by a graphical representation of the data.

The study was designed in a Retrospective manner. It was conducted in patients admitted in the Neonatal intensive care unit of Government district headquarters hospital, Thirupur district (Tamilnadu) from September 2017-Februvary 2018.

A study population of 80 patients (all below 4 weeks and diagnosed with Neonatal sepsis) was selected.

++-+SEX WISE DISTRIBUTION OF NEONATAL SEPSIS

TABLE 1

SEX	FREQUENCY n=80	PERCENTAGE %
MALE	44	55
FEMALE	36	45

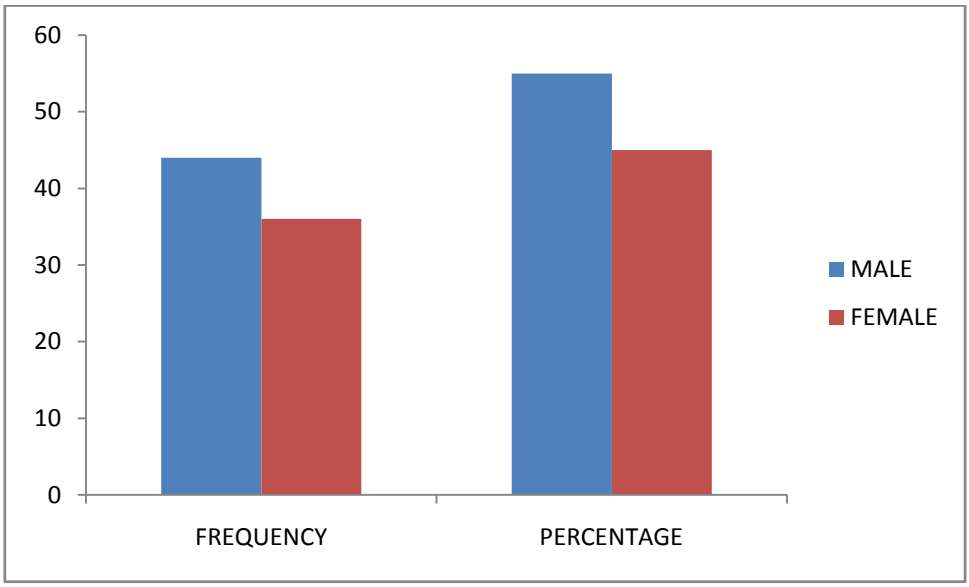


FIGURE 1

BODY WEIGHT DISTRIBUTION OF NEONATAL SEPSIS CASES

TABLE 2

BODY WEIGHT (kg)	FREQUENCY (n=80)	PERCENTAGE %
NORMAL BODY WEIGHT	36	45
LOW BODY WEIGHT	42	52.5
VERY LOW BODY WEIGHT	2	2.5

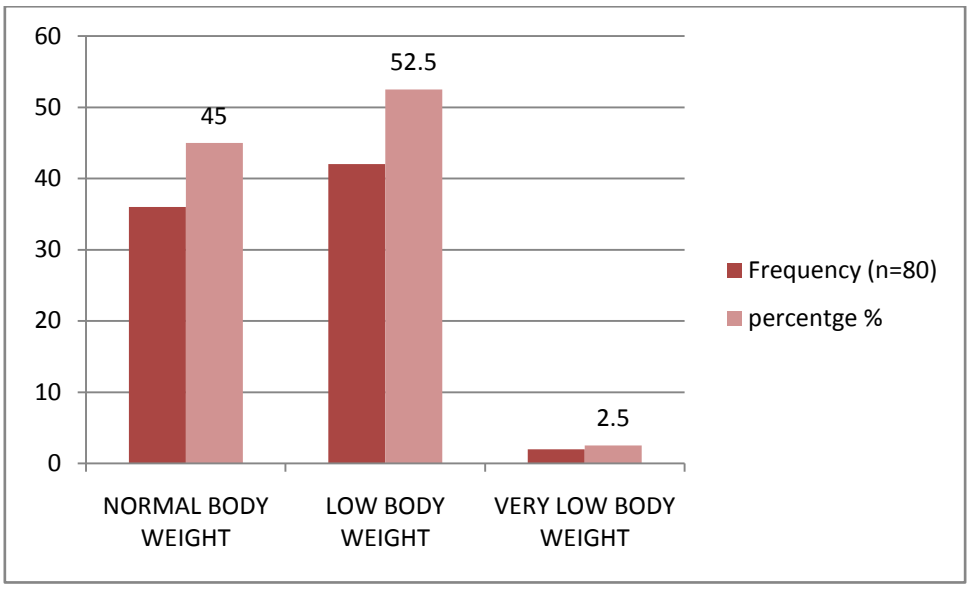


FIGURE 2

Normal body weight >2.5kg

Low body weight 1.5to2.5kg

Very low body weight >1.5kg

DISTRIBUTION OF GESTATIONAL AGE OF NEONATAL SEPSIS

TABLE 3

GESTATIONAL AGE (WEEKS)	FREQUENCY (n)	PERCENTAGE %
Term	39	48.75
Near term	18	22.50
Pre-term	23	28.75

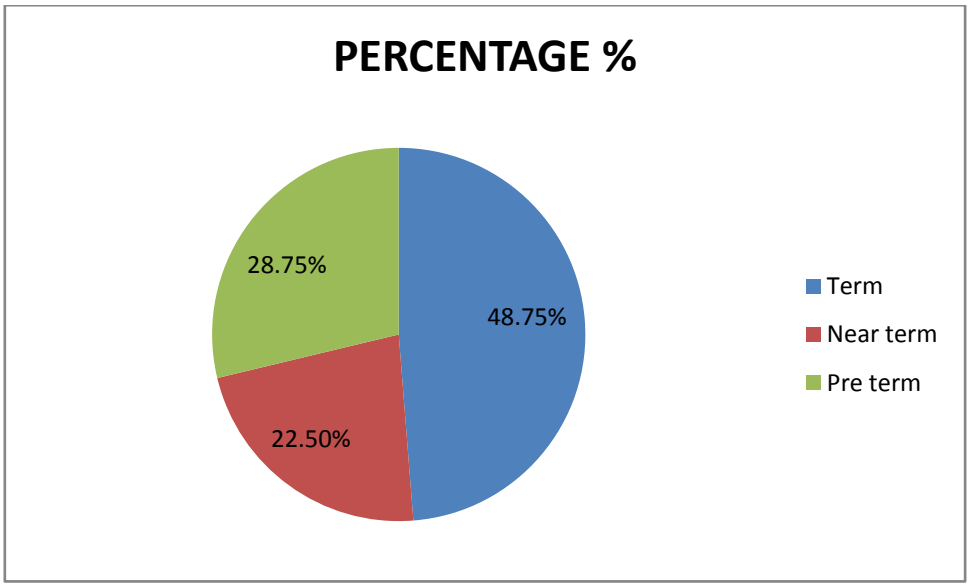


FIGURE 3

Term >37 weeks

Near term 35-37 weeks

Pre term<35 weeks

PREVALENCE OF SYMPTOMS IN NEONATAL SEPSIS PATIENTS

TABLE 4

SYMPTOMS	NUMBER OF PATIENTS	PERCENTAGE %
Reduced sucking	32	40
Respiratory distress	19	23.75
Fever	15	18.75
Yellowish discolouration	6	7.5
Increased irritability	3	3.75
Lethargy	2	2.5
Convulsions	2	2.5
Vomiting	1	1.25

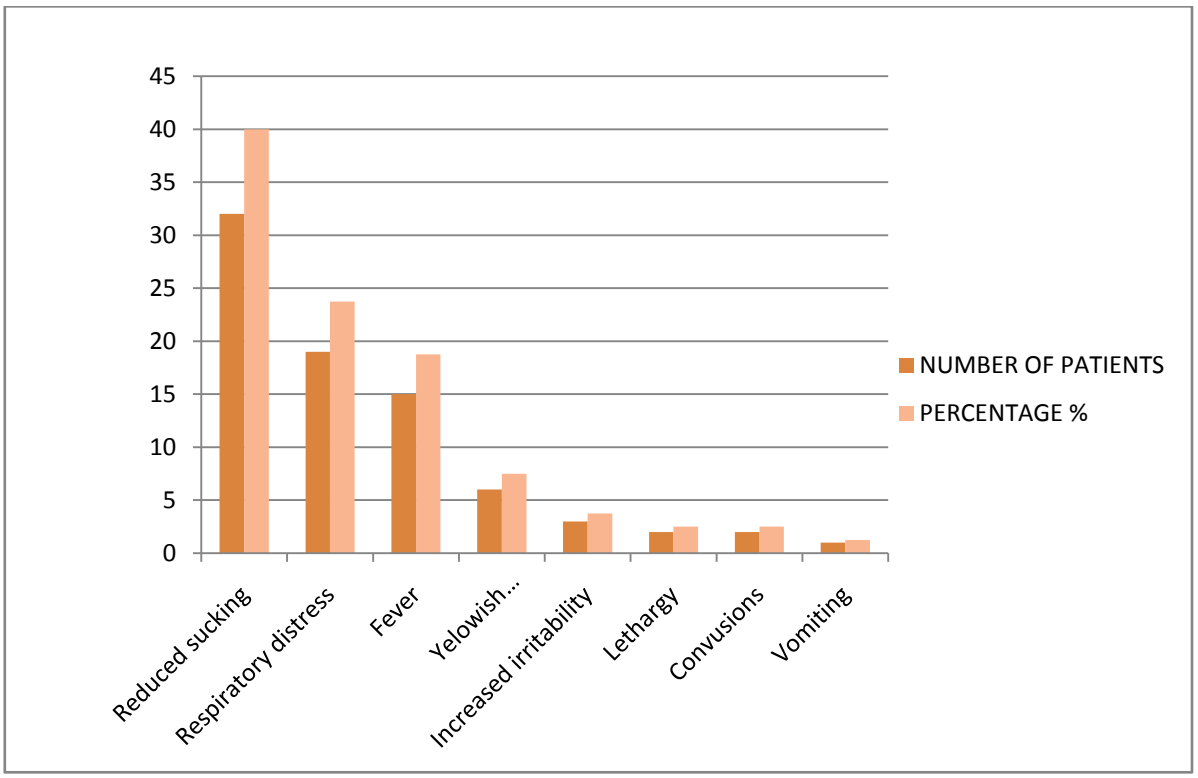


FIGURE 4

PREVALENCE OF RISK FACTORS IN NEONATAL SEPSIS PATIENTS

TABLE 5

RISK FACTORS	NUMBER OF PATIENTS (n)	PERCENTAGE %
Low birth weight	42	52.5%
Prematurity	41	51.25%
Fever	15	18.75%
Asphyxia	10	12.5%
Meconium aspiration	5	6.25%

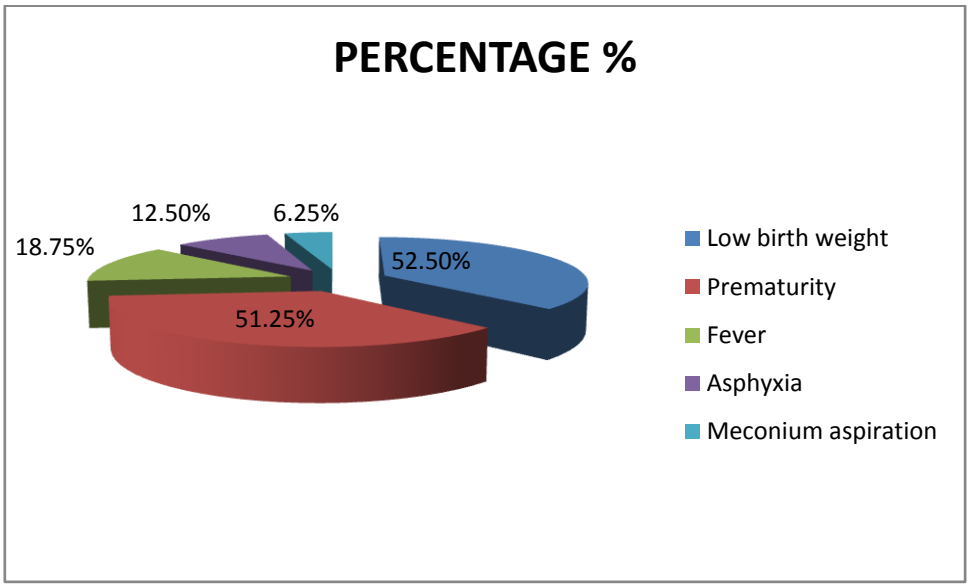


FIGURE 5

DURATION OF TREATMENT OF NEONATAL SEPSIS

TABLE 6

DURATION OF TREATMENT	NO OF PATIENTS	PERCENTAGE %
0-4 DAYS	8	10
4-8 DAYS	50	62.5
8-14 DAYS	22	27.5

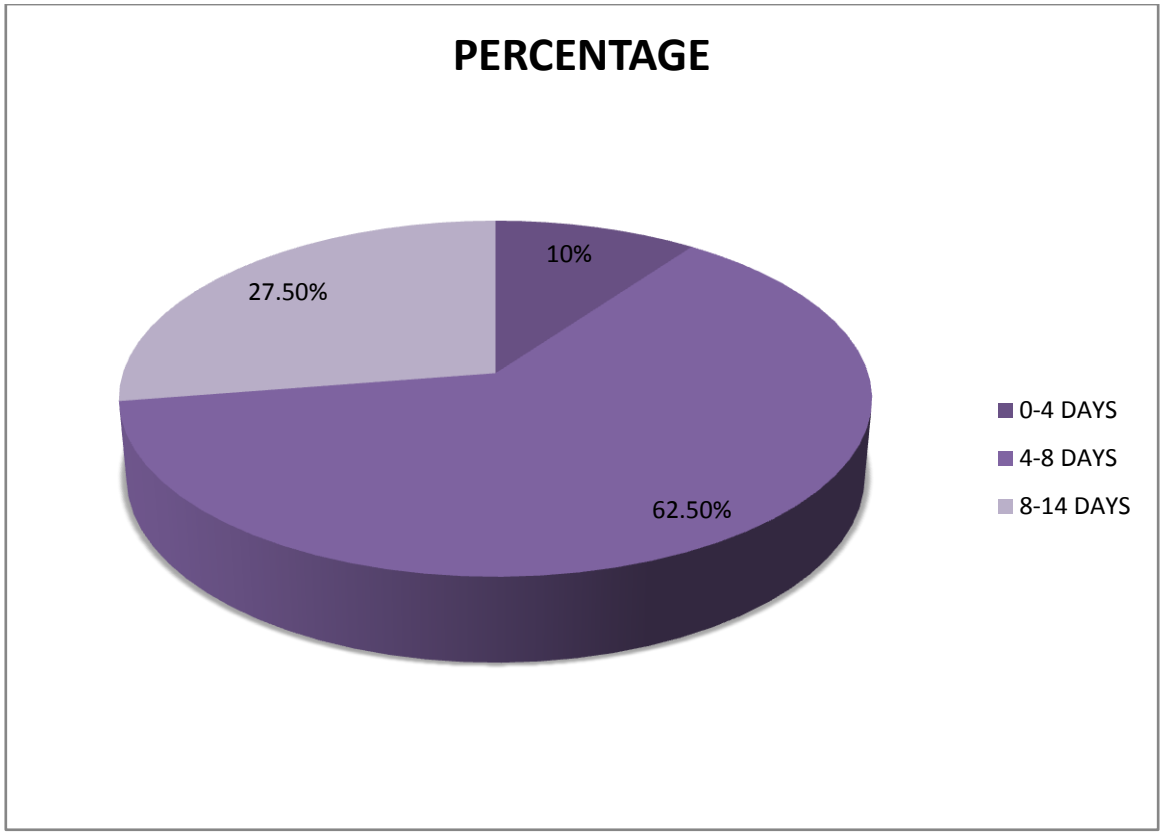


FIGURE 6

DRUG PATTERN IN TREATMENT OF NEONATAL SEPSIS

TABLE 7

MEDICATION	NO OF PATIENTS	PERCENTAGE %
Ampicillin	64	80
Gentamycin	66	82.5
Cefotaxime	52	65
piperacillin	8	10
Amikacin	48	60

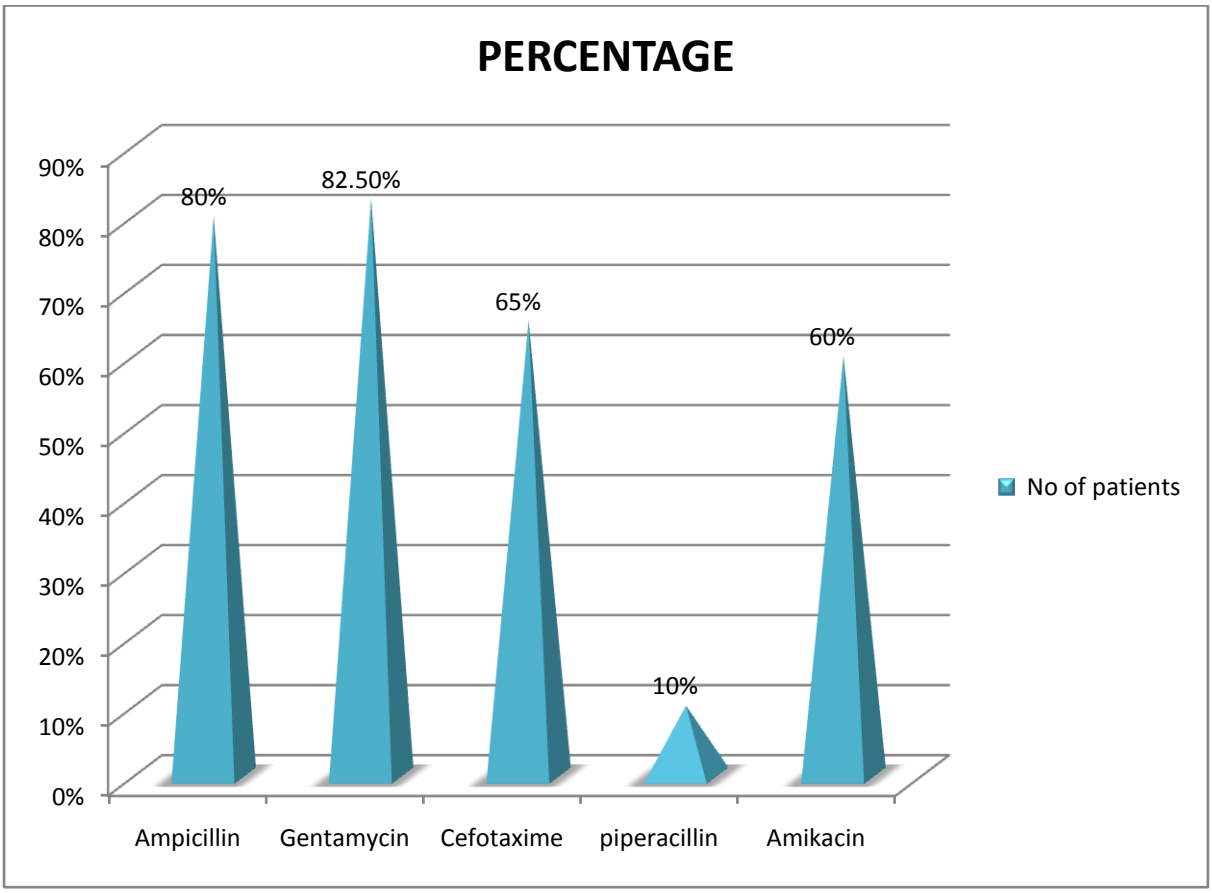


FIGURE 7

PERCENTAGE OF GIVEN DOSE OF AMPICILLIN

TABLE 8

Ampicillin dose (mg)	No of patients (n=64)	Percentage%
80 mg	8	12.5%
90 mg	6	9.37%
100 mg	6	9.37%
110 mg	4	6.25%
120 mg	4	6.25%
130 mg	2	3.12%
140 mg	8	12.5%
150 mg	16	25%
160 mg	8	12.5%

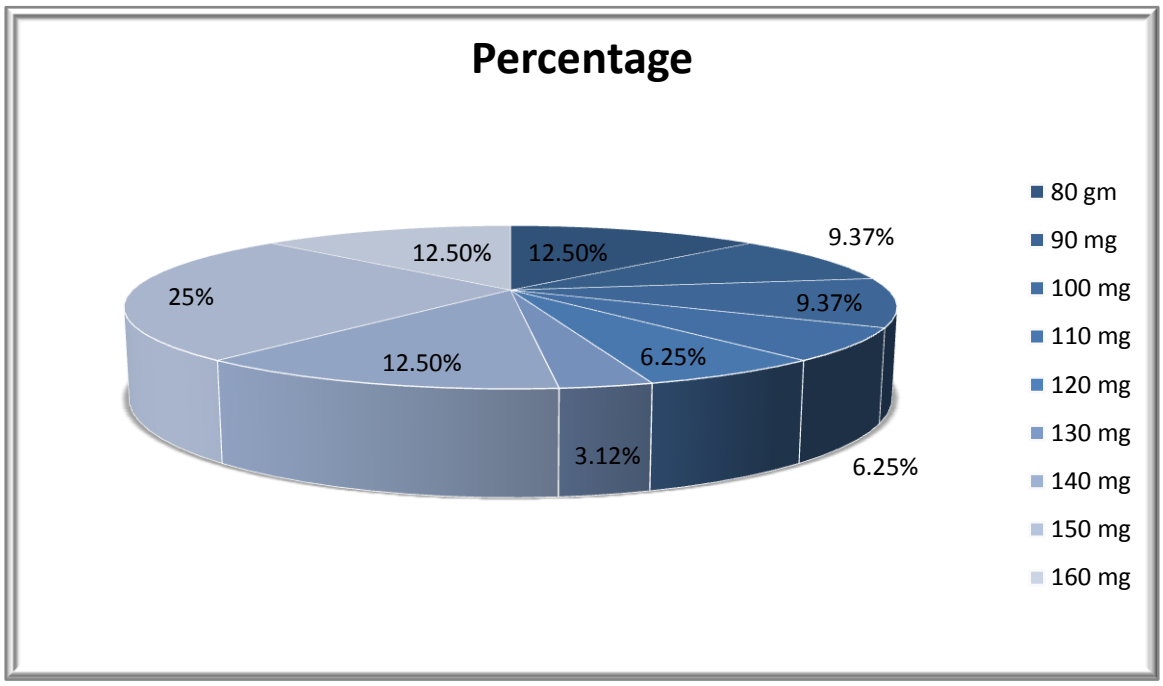


FIGURE 8

PERCENTAGE OF GIVEN DOSE OF GENTAMYCIN

TABLE 9

Gentamycin dose (mg)	No of patients (n=66)	Percentage%
7 mg	4	6.06%
8 mg	10	15.15%
9 mg	6	9.09%
10 mg	8	12.12%
11 mg	4	6.06%
12.5 mg	6	9.09%
13 mg	4	6.06%
14 mg	16	24.24%
16 mg	8	12.12%

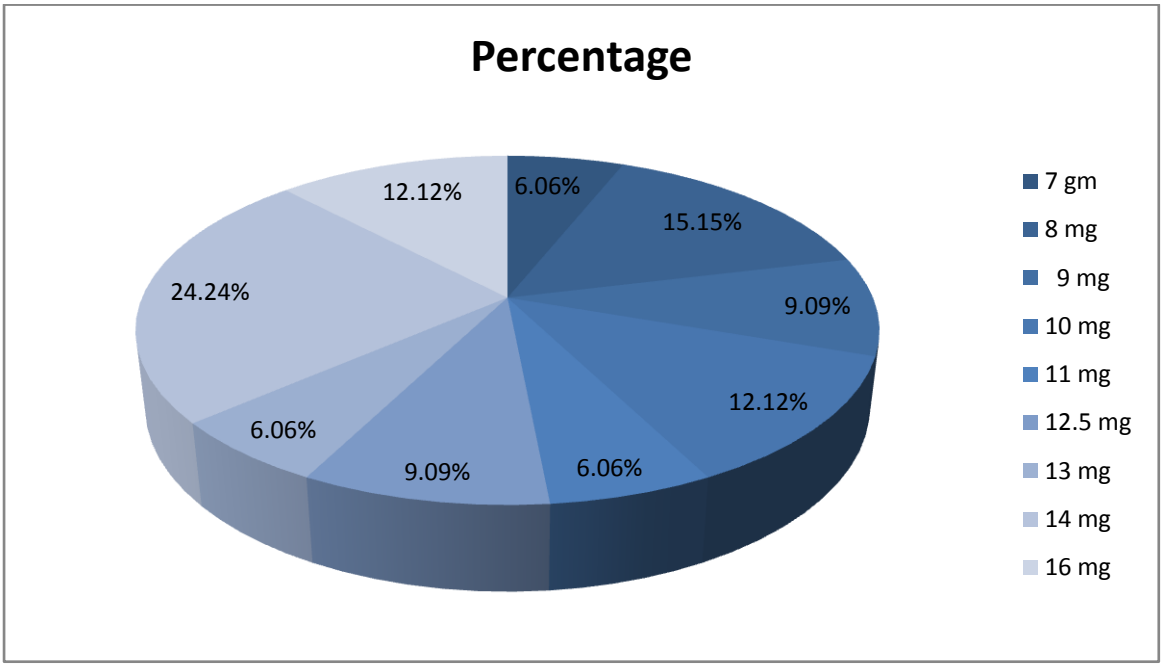


FIGURE 9

PERCENTAGE OF GIVEN DOSE OF CEFOTAXIME

TABLE 10

Cefotaxime dose (mg)	No of patients (n=52)	Percentage%
80 mg	9	7.69%
90 mg	10	19.23%
110 mg	6	11.53%
125 mg	8	15.38%
150 mg	16	30.76%
160 mg	9	7.69%
175 mg	2	3.84%
200 mg	2	3.84%

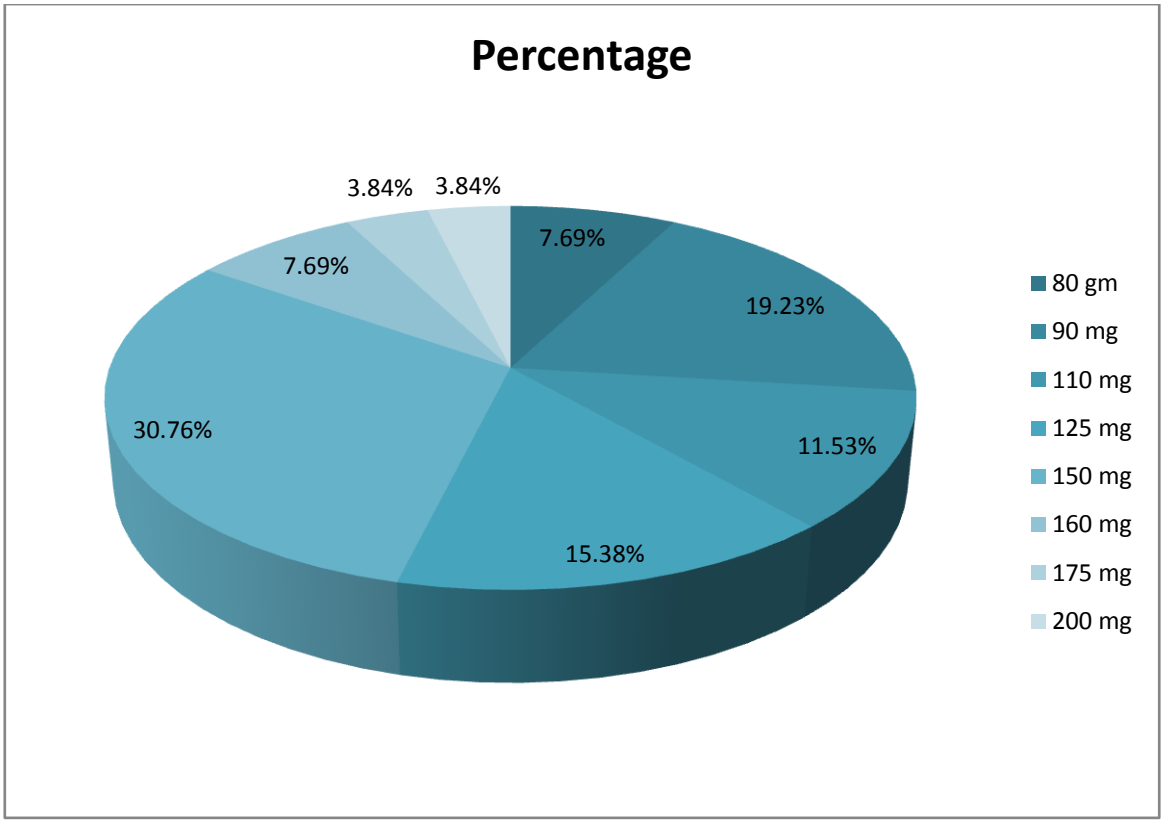


FIGURE 10

PERCENTAGE OF GIVEN DOSE OF AMIKACIN

TABLE -11

Dose of Amikacin (mg)	No of patients (n=48)	Percentage%
12.5mg	6	12.50%
20mg	6	12.50%
22 mg	2	4.16%
24 mg	2	4.16%
30 mg	2	4.16%
35 mg	12	25.00%
40 mg	2	4.16%
45 mg	14	29%
60 mg	2	4.16%

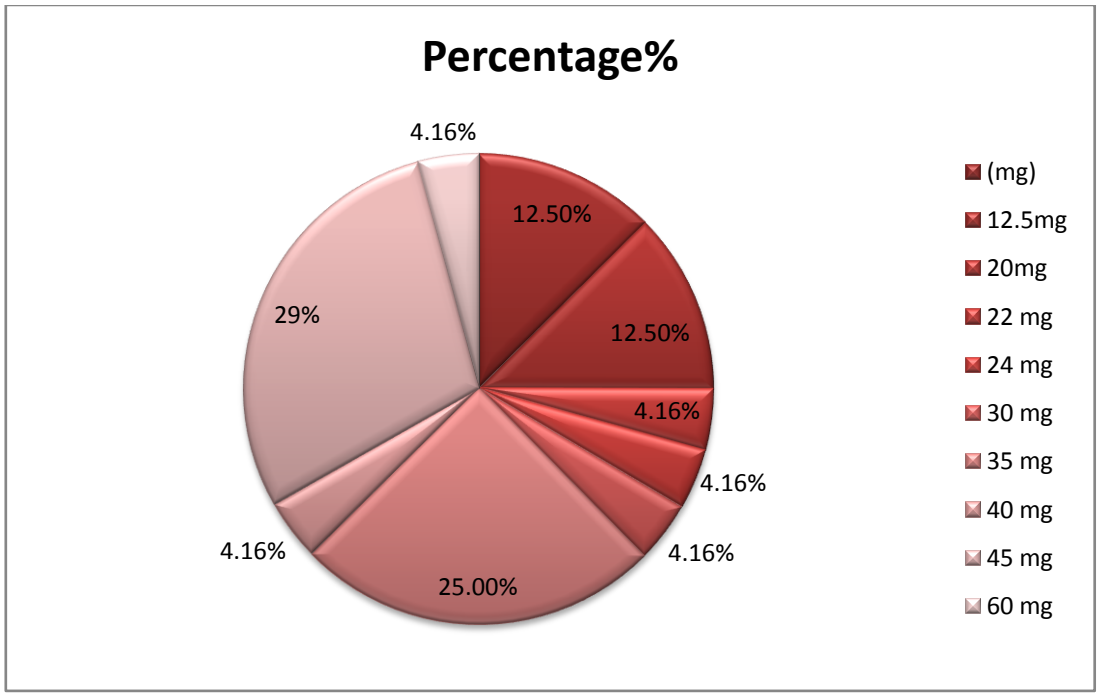


FIGURE 11

DISCUSSION

- 80 Patients were selected for the retrospective study. The study population consisted of 44 Males (55%) and 36 Females (45%) FIGURE 1.
- Patients selected for the study had different body weight distributions. Most of the patients affected had low body weight (52.5%) and then followed by neonates with normal body weight (45%) and neonates with very low body weight (2.5%). FIGURE 2.
- Maximum number of patients fall on the gestational age group of more than 37 weeks (term)(48.75%). In both males and females maximum number of patients were from this age group. Minimum number of patients were from the age group of 35 to 37 weeks (Near term) (22.5%)and (28.75%) Patients with gestational age of less than 35 weeks (Pre term) was affected with neo natal sepsis. This indicates that incidence of Neonatal sepsis increases with gestational age. FIGURE 3
- The most common symptom associated with neonatal sepsis was found to be 'Reduced sucking' (40%) followed by 'Respiratory distress" (23.75%) and then followed by 'Fever' (18.75%) and 'Yellowish discolouration' (7.5%) . Some other symptoms such as 'vomiting' (1.25%) and 'convulsions' (2.5%) and 'Lethargy' (2.5%) and 'Increased irritability' (3.75%) were found to be minimum. FIGURE 4.
- The most common risk factors associated with Neonatal sepsis was found to be 'Low birth weight' (52.5%) and prematurity (51.25%).Both risk factors were found in more than half of the study population. FIGURE 5
- The distribution of duration of treatment of neonatal sepsis was found to be high in 4 to 8 days (62.5%) 50 out of 80 patients were treated for this duration of time. Minimum duration of treatment was found to be 0 to 4 days (10%) only 8 patients were treated for this period of time and (27.5%) of patients were treated for a duration of 8 to 14 days. FIGURE 6.
- Ampicillin and Gentamycin were the most commonly used antibiotic medication. Gentamycin was used in 66 patients (82.5%) and Ampicillin was used in 64 patients (80%).
- Cefotaxime was used in 52 patients (65%) and amikacin was used in 48 patients and piperacillin was used in 8 patients(10%) out of 80. FIGURE 7.

- Most commonly used dose of Ampcillin was found to be 150mg (25%) it was used in 16 times in 64 patients prescribed with Ampicillin .Followed by140mg,160mg,80mg(12.5%) of Ampicillin was used 8 times in 64 patients. And 90mg and 100mg (9.37%) of Ampicillin was prescribed in 6 patients and 110mg and 120mg (6.25%) of Ampicillin was prescribed in 4 patients.130mg (3.12%) was the least prescribed dose of Ampicilin it was prescribed only in 2 patients in 64 patients prescribed with Ampicillin. FIGURE 8.

- Most commonly used dose of Gentamycin was found to be 14mg(24.4%) it was use in 16 times out of 66 patients prescribed with Gentamycin and 8 mg (15.15%) was prescribed for 10 patients out of 66 patients prescribed with Gentamycin.16mg and 9 mg (12.12%) of Gentamycin were prescribed in 8 patients . Followed by 12.5mg and 9 mg (9..09%). The most less used doses of Gentamycin was found to be 7mg,11mg,13mg (6.06%) were only used in 4 patients out of 66. FIGURE 9.
- Most commonly used dose of Cefotaxime was found to be 150mg (30.76%) wasprescribed for 16 patients in 52 patients prescribed with Cefotaxime. And 90 mg of Cefotaxime was used in (19.23%) of the patients followed by 125mg (15.38%) and 110mg (11.53%) in total of 52 patients. 175mg (3.84%) and 200mg(3.84%) was found to be used very rarely it was used only in 2 patients. 80mg (7.69%) of Cefotaxime was found to be used in 4 patients. FIGURE10.

- Most commonly used dose of Amikacin was fund to be 45mg (29%) was used in 14 patients out of 48 patients prescribed with Amikacin. 35mg(25%) was prescribed for 12 patients and 12.5mg and 20 mg (12.5%) was prescribed for 6 patients. The remaining doses of Amkacin 22mg (4.16%),24 mg (4.16%), 30mg (4.16%), 40mg (4.16%),60 mg (4.16%) of Amikacin was the lesser used doses and was used only in 2 patients . FIGURE 11.

CONCLUSION

- Neonatal sepsis was found to be more prevalent in males rather than female patients. This indicates that male gender is an important risk factor for Neonatal sepsis.
- Prevalence of Neonatal sepsis found to be increasing in patients with low birth weight comparing to those patients having normal birth weight.
- Neonatal sepsis was found to be more prevalent in neonates of gestational age group more than 38 weeks. This reflects that gestational age is an important risk factor for Neonatal sepsis.
- Most common symptom associated with neonatal sepsis was found to be Reduced sucking, about 40% of population had Reduced sucking.
- Some other symptoms like Respiratory distress and Fever was also found to be the common symptoms of Neonatal sepsis.
- The most common risk factors associated with Neonatal sepsis were found to be low birth weight and prematurity. These two risk factors were found in more than half of the population. Chances for neonatal sepsis was found to be increasing with these risk factors.All the population had multiple risk factors.
- Most population were treated for a time period of 4 to 8 days about (62.5%)of patients out of 80 were under gone treatment for this period. Treatment for 8 to 14 days were limited to (27.5%).
- The drug pattern included was antibiotics along with vitamin k injection in some cases.
- Most preferred treatment was antibiotics. Ampicillin and Gentamycin were the most commonly used antibiotics. These two are generally used as the first line treatment of Neonatal sepsis. Combination therapy was preferred more than treatment with individual drugs.
- The combination of Ampicillin + Gentamicin followed by Cefotaxime + Amikacin is found to be an appropriate choice for empirical therapy of neonatal sepsis.
- Most commonly used dose of Ampicilin was found to be 150mg.
- Most commonly used dose of Gentamycin was found to be 14mg.
- Most commonly used dose of Cefotaxime was found to be 150mg
- Most commonly used dose of Amikcin was found to be 35 mg.

- The present study demonstrates high prevalence of Neonatal sepsis risk factors in the population.The incidence of Neonatal sepsis is likely to increase further so there is need to conduct awareness programmes regarding the disease.
- Many newborns receive prolonged antibiotic therapies without considering the adverse effects and also it may result in antibiotic resistance. So we need to develop guidelines to manage individuals with neonatal sepsis.

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PROFORMA

PATIENT DETAILS

NAME: IP NO.:
AGE: days SEX: M/F
DOB: / /
GESTATIONAL AGE:
BIRTH WEIGHT:
CHIEF COMPLAINTS:
DIAGNOSIS:

OUTCOME OF HOSPITALIZATION: Survived
Died
Unlnown

MOTHER'S DETAILS

NAME:
AGE:
BLOOD TYPE:
PARA AND GRAVIDA:
TYPE OF DELIVERY:
PAST MEDICAL HISTORY:

PAST MEDICATION HISTORY:
PREVIOUS COMPLICATIONS OF PREGNANCY:

PRESENCE OF ANY OF THE FOLLOWING: **Y/N**

- Meconium stained liquor
- Low birth weight <2.5 kg
- Prematurity <37 weeks
- Premature rupture of membranes
- Amnionitis
- Three per vaginal examinations during labour
- APGAR Score <7
- CRP > 5 mg/L
- Urinary tract infection of mother during pregnancy

PRESENC EOF ANY OF THE FOLLOWING SYMPTOMS: **Y/N**

- Reduced sucking
- Swelling
- Diarrhoea
- Fever
- Increased irritability
- Decreased urination

General physical examination:

Wt: Icterus:

Color: Abdomen:

Vital signs:

Temp: HR:

RR:

Laboratory investigations:

Hb : TWC:

Platelet count: CRP:

Blood culture:

DRUG CHART

SL NO:	NAME OF DRUG	DOSE	ROA	FREQUENCY	DURATION

INFORMED CONSENT

Participant written informed consent

I understand that my participation is voluntary and that I may withdraw from this study at any time without giving any reason or to decline to answer any particular question in the study. I consent the members of the study to have access to my response and to publish the result, provided my identity is not revealed. I voluntarily agree to participate in the study.